RECENT ADVANCES IN CANCER THERAPY*

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FROM time to time it is useful to review in our own scientific circle the status of cancer therapy. The reports of "spectacular" therapeutic advances in the daily press are, unfortunately, not only unreliable but harmful. Progress in cancer therapy is not as dramatic as progress in cancer research. The laboratory worker, some fine morning in May, finds ten of his mice with tumors induced by nucleo-protein that he has prepared by careful precipitation and concentration, and he has a discovery. The clinician, on the other hand, compares, through a long period of years, the results of tedious and varied methods of treatment. His conclusions are based to a great degree upon the breadth of his experience and the soundness of his common sense, rather than upon close reasoning. He is often faced with a choice between two poor methods of treatment, and must take care at least to do no harm. Thus, I must ask your indulgence tonight if I state our therapeutic attitude in somewhat general terms, without documentation at every point.

It is of interest to review for a moment the history of our therapeutic attack on cancer. Looking backward fifty years to Halsted's day, we find the masters of surgery developing the techniques of the radical surgical attack on cancer. These courageous surgeons had many handicaps. One of the most serious was the lack of a practical method of immediate microscopical diagnosis. They had to rely on gross pathology which now and then betrayed them. And they had a distressingly high operative mortality. Surgery in those days was often truly heroic.

It is no wonder that many turned hopefully to radiation when it became generally available about twenty-five years ago. The deceptively favorable initial response to radiation of some types of cancer, such as epithelioma of the skin, raised almost everyone's hopes that radium or x-rays could be developed to the point of controlling most forms of

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cancer. A man of high idealism and great good will like James Ewing could carry on what amounted to a crusade for radiation. This wave of enthusiasm for radiation led to its use for all types of neoplasms, and the evolution of many ingenious methods of applying it.

Unfortunately, these high hopes of a generation ago in the curative value of radiation were dissipated as knowledge of its effects accumulated and the end results became available.

Today it is clear that except for a few types of cancer such as some forms of epithelioma of the skin, epithelioma of the larynx, and epithelioma of the cervix, radiation can not compete with surgery as a curative agent. This period of disillusionment in the curative value of radiation carried us into the 1930's, and the period preceding the recent war.

Although our experiments with radiation left many of us chastened, they taught us important lessons. First, they revealed the great usefulness of radiation as a palliative form of treatment. From this palliative standpoint alone radiation has won for itself an important and lasting place among the weapons which every properly equipped hospital must possess. Trained radiotherapeutists are an essential part of any organization attempting to treat cancer today. Radiation checks temporarily several types of malignant disease in which surgery is futile. Lymphoblastomas and the highly malignant epitheliomas of the posterior tongue and pharynx are examples. It brings relief to many suffering with metastases from breast cancer.

A second gain from our period of enthusiasm for radiation has been the development of specialization in cancer. It is a historical fact that the cancer clinics in which radiotherapy evolved, the Radium Institute in Paris, the Radiumhemmet in Stockholm, and our Memorial Hospital, have also become the leading centers for training specialists in cancer diagnosis and treatment. James Ewing was a firm believer in specialization in cancer and we can thank him for what progress has been made in gaining recognition for our specialty in this country.

As with most other modern complex fields of knowledge, specialization in cancer has been fruitful. It has led to improved diagnosis and more expert care of the patient. The public and a large section of the medical profession are well aware of this fact, and cancer hospitals and cancer clinics are handling a constantly increasing share of the cancer patients.

Despite all this the medical schools and teaching hospitals have not given our specialty much recognition. The academic mind continues to resist new forms of specialization despite the fact that the rapidly increasing complexity of modern science makes specialization as inevitable as tomorrow's sunrise. In any good hospital clinic on any day one sees a wide variety of specialists excelling in their knowledge of the diseases in which they are specially interested. A man who spends the mature years of his life studying one disease naturally comes to know more about it than his colleagues who dissipate their efforts. If he happens to be an able technician he develops a superior surgical technique. But his technical skill is the least important of his advantages. If he has had a broad general training before specializing, and if he is a man of intelligence, he will draw upon knowledge from the fundamental sciences and from every field of medicine and surgery and apply it in his intensive study of the disease in which he specializes. It is not just to stigmatize such a man as a narrow specialist in technique.

Although the traditional conservative point of view that the general surgeon can treat the various types of cancer equally well still prevails in academic circles, there are signs of a beginning awareness of the advantages of a degree of specialization in cancer. It is becoming apparent that the surgeon who ecels in abdominal surgery and is of necessity an expert in gastrointestinal physiology, may treat cancer of the stomach and bowel with great skill; yet he may not do as well with the tedious and radical dissections required for cancer occurring elsewhere in the body, for example in the mammary gland, where a knowledge of pathology is more fundamental. There is need for all our skills in dealing with such a formidable enemy as cancer, and no one man can encompass them all. Let us by all means aim first at what is best for the patient and forget tradition.

To continue our historical review we come to the present trend in cancer therapy. It might be called the surgical epoch. During the last ten or fifteen years advances in certain of the fundamental aspects of surgery have made it so much safer that it is today possible to attack cancer far more vigorously. Improved anesthesia today permits the surgeon to operate for a far longer period of time without excessive shock. Operating on the surface of the body we can work comfortably for five or six hours. This permits us to do much more thorough and better dissections. It is fair to say that this improvement in anesthesia

has been the most important single factor in the recent rapid development of thoracic surgery and the attack on lung cancer.

The improved facilities for blood transfusion have also been of much assistance to the surgeon in his attack on cancer, for they have certainly lowered the mortality from operative shock.

The abdominal surgeon has found a strong defence against his old enemy, intestinal obstruction, in the use of the Abbott tube. Abbott is gone, struck down himself by malignant disease, but his discovery is saving lives every day of patients who have had gastric or bowel resections for cancer.

The frequency of local recurrence following many types of operations for cancer that have been done in the past can leave no doubt about the desirability of surgeons taking advantage of their newly found technical advantages. Our course, indeed, is clear. In many forms of cancer where radiation has failed to cure or has given only a limited percentage of cures, and where a more radical surgical attack is possible, we must have the courage to develop it, no matter how mutilating it may be. This, we might say, is our present temper.

The surgeon who today faces the grave responsibility of carrying out a mutilating operation for cancer has one solid advantage over his predecessor of Dr. Halsted's era: he has the surgical pathologist by his side to assist him in making certain of the diagnosis and to advise him as to the extent of the dissection. Fifty years ago surgical pathologists did not exist and the frozen section method of making an immediate microscopic diagnosis had not been developed. It was, in fact, in 1905 that Wilson of the Mayo Clinic began to use it. Dr. Halsted and his contemporaries had to depend upon their clinical impressions and their knowledge of gross pathology in diagnosis. We know that every now and then, particularly for lesions of the mammary gland, these evidences are delusive. Dr. Bloodgood, as a matter of fact, once wrote in an account of his early days in Halsted's clinic that 10 per cent of the benign lesions of the breast were mistaken for carcinoma and radical mastectomy needlessly done.

Thanks to the methods of immediate microscopical diagnosis which surgical pathologists have since perfected, this kind of mistake need never occur today. The frozen section method of diagnosis is the one which Dr. Stout and I have found to be the most desirable, and we have no evidence that the careful excision for frozen section of a tiny

wedge of tissue measuring only a few millimeters in size, from the superficial aspect of the lesion, is harmful. Others prefer the aspiration method of diagnosis. No matter which method is used the surgical pathologist has rescued us surgeons from the sea of doubt and set our feet on solid ground.

Equally important is the fact that the surgical pathologist is our guide in planning the extent and the nature of our attack on cancer. His microscope is a measure of how it extends and metastasizes. A great many patients come for treatment so late that their lesions are inoperable, or to put it another way, surgery will do more harm than good. This decision depends primarily upon a knowledge of surgical pathology.

At Columbia, A. P. Stout, as surgical pathologist, Maurice Lenz, as radiotherapeutist, and John Hanford and I as surgeons, have formed a team in attacking cancer. We see the patients together in the outpatient Neoplasm Clinic, and advise regarding problems arising on the wards and in the operating room. We keep special records of certain types of cancer cases, and from time to time review our therapeutic results. In this kind of team each member must know a good deal about the other's specialty, if there is to be a genuine meeting of minds. The surgical pathologist should have been trained in clinical surgery, and the surgeons and the radiotherapeutists should have had an apprenticeship in surgical pathology.

There is today in this country a great shortage of surgical pathologists and of funds with which to pay them. They are keymen in a cancer clinic. Surgeons and radiotherapeutists gain their income from private practice, but the surgical pathologist is traditionally an employee of the hospital in which he serves, and his salary is notoriously inadequate. Hospitals in which there is no surgical teaching tend to skimp or do without pathology. Men of ambition and talent will be attracted to the specialty only when there is promise of better salaries. If I were asked today what single kind of subsidy on the part of the Federal government would do the most to improve cancer therapy throughout the country, I would say "A fund providing fellowships to train surgical pathologists, and adequate salaries for men properly trained in the specialty, in key hospitals in every community." The cancer clinics which are springing up everywhere now-a-days would be tremendously helped by this kind of subsidy for surgical pathologists.

CANCER

AVERAGE ANNUAL INCIDENCE RATES PER 100,000 POPULATION
NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY
1942-1943-1944

ORDER OF INCIDENCE	SITE	SEX	ANNUAL INCIDENCE
1	BREAST	FEMALE	60.0
2	CERVIX UTERI	FEMALE	34.3
3	SKIN	MALE	29.2
4	STOMACH	MALE	27.1
5	COLON	FEMALE	24.4
6	PROSTATE	MALE	23.2
7	SKIN	FEMALE	19.8
8	COLON	MALE	19.6
9	STOMACH	FEMALE	17.6
10	RECTUM & RECTOSIGMOID	MALE	15.2
11	LUNG	MALE	14.7
12	OVARY	FEMALE	12.2
13	RECTUM & RECTOSIGMOID	FEMALE	12.1
14	FUNDUS UTERI	FEMALE	11.9
15	BLADDER	MALE	11.5
16	LIP	MALE	6.8
17	LEUKEMIA	MALE	6.3
18	PANCREAS	MALE	5.7
19	LIVER	FEMALE	5.5
20	BLADDER	FEMALE	5.2

ALL SITES FEMALE - 270.8 ALL SITES MALE - 231.8

TABLE I

Having reviewed the general trend of cancer therapy it is of interest to speak briefly of the current view regarding the treatment of the most frequent special types of malignant disease, illustrating, as we go along, some of the general conclusions that we have drawn.

I should like first to call your attention to Table I which shows in graphic form the recent morbidity data for cancer in New York State compiled by Dr. Morton Levin of the State Department of Cancer Control. These data are unique, I believe. They have been collected with great care from hospitals, doctors, and public health agencies. They provide, for the first time, a fairly accurate picture of the true comparative incidence of the various types of cancer. This order of incidence is rather different than the impression which those of us who work entirely in hospitals have had. Cancer of the breast is by far the most frequent type, being almost twice as common as any other form of cancer. Cancer of the cervix is next in order, followed by cancer of the skin in males. Cancer of the stomach in males is fourth in order. Cancer of the colon in females is fifth, cancer of the prostate is sixth in order. Cancer of the skin in females is seventh. Cancer of the colon in males is eighth. Cancer of the stomach in females is ninth. Cancer

of the rectum and rectosigmoid in males is tenth. Cancer of the lung, which appears to be the only form of cancer that is actually increasing, is far more common in males than in females, and in our chart it is eleventh in order. Cancer of the ovary is twelfth. Cancer of the rectum and rectosigmoid in females is thirteenth, and cancer of the fundus of the uterus is fourteenth. Cancer of the bladder in males is fifteenth. The remaining forms of cancer are considerably less frequent, and need not occupy us here.

Cancer of the Breast

Cancer of the breast presents a diagnostic problem that requires expert clinical and pathological judgment. The public has been pretty well convinced that a tumor in the breast requires surgical investigation. Not so all doctors. There is appalling evidence that our medical education is not fitting physicians to meet this diagnostic problem. In a series of cases which we have recently studied from the viewpoint of who was responsible for the delay in diagnosis we found that the patient was to blame in 63 per cent of the cases, but some physician was to blame in 27 per cent. These cases are all ones in which the patient had discovered her own tumor and went for advice concerning it. She was told that it was harmless, or given some kind of placebo, or told to return for re-examination at a distant date. She was *not* told that she might have a cancer and that she must enter a hospital promptly for diagnosis and treatment. In this series of patients the consequent delay between the time the patient received the bad medical advice and the time correct treatment was begun averaged 59.6 weeks. We know that a delay of more than six months in cancer of the breast cuts the cure rate in half.

These facts force us to conclude that the most important thing that we can do to improve results in cancer of the breast is to pound into our students and interns the simple and fundamental rule that any tumor of the breast, no matter how innocuous it may seem to be, must be regarded as possibly being a carcinoma. The patient should be admitted to a hospital promptly, all preparations made for a radical mastectomy, and the nature of the lesion proved microscopically. It would appear that we are more in need of education of physicians than of the public in cancer diagnosis. One would like to see the funds recently subscribed by the public for cancer control devoted to providing

graduate training for physicians rather than for propaganda to the public.

Cancer of the breast is one of the types of cancer in which radiation has been extensively tested. About ten years ago we carried out a clinical experiment with radiation in this disease which has given us evidence that has led us to conclusions which are fundamental for us. A series of patients with operable and borderline carcinomas were treated intensively with radiation by Dr. Lenz. The total amount of radiation given to these cases was in general as large as the modern divided dose technique permitted. Several months were required to complete it. After a suitable delay to permit recovery from the acute radiation reaction radical mastectomy was done. In every one of these cases careful microscopical study of the specimen revealed persisting carcinoma cells. These cells usually show signs of having been severely injured by the radiation, and they lie locked up in a dense fibrous stroma. We assume, however, that they are alive and capable of renewed growth. Clinical experience supports this assumption, for we have repeatedly seen carcinomas of the breast that regressed initially following intensive radiation, remained quiescent for two, three, four, or even five years, and then began to grow again. These facts have led us to conclude that radiation will not *cure* carcinoma of the breast, and we have given it up in the disease except as a palliative agent. We do not use it prophylactically as an aid to surgery because operation alone is highly efficient in controlling the local disease, and we have no reason to believe that radiation to the operative field has any effect upon the incidence of distant metastases, our bête noir in breast cancer,

Having been forced by the failure of radiation to rely for *cure* entirely upon radical mastectomy we have attempted to use the operation more critically. Dr. Stout and I have recently worked out criteria of operability. We have found that there are certain types of breast carcinoma that are never cured by surgery. These include the inflammatory type of breast cancer, cases with extensive edema of the skin of the breast, and most cases in which the tumor is solidly fixed to the chest wall. We believe that operation in these cases not only fails to cure but actually shortens life by hastening metastases. In these inoperable cases radiation is the preferred method of treatment, and Dr. Lenz has sometimes succeeded in arresting the disease for as long as five years.

Where breast cancer is operable we believe in performing the

most radical operation that can be done. With modern surgical technique we have been able to extend the original Halsted operation. We remove so much tissue that a large Thiersch graft is required to cover the defect on the chest wall. Our operation requires 5 or 6 hours to carry out, but when done with proper care it has a negligible mortality and it does not cripple the arm. Comparisons in our own hospital indicate that this truly radical operation gives only half as many local recurrences, and a 50 per cent higher five-year cure rate than the usual so-called radical mastectomy. This improvement is no doubt due in part to our more critical selection of cases for operation.

These, we believe, are our best hopes for improving the results with carcinoma of the breast. In younger women sterilization, and in older women the administration of estrogens or androgens, occasionally check the progress of bone metastases temporarily, and in rare cases have been known to retard the advance of the primary tumor. These hormonal agencies, however, are not to be regarded as of much practical importance in the control of breast cancer. Their effects are too inconstant and too feeble to make them rivals of radiotherapy. When they are used as supplements to radiation it is difficult to assess their real value.

Cancer of the Cervix

Carcinoma of the cervix has slightly more than one-half the frequency of breast carcinoma. From the causative standpoint there is one remarkable feature about the disease that gives hope that its incidence can be cut down. This is the fact emphasized by Twombley, that cervix cancer is extraordinarily rare among Jewish women whose husbands have been circumcised. We know also that it is a disease of the under-privileged among whom baths are not in general as available as among the well-to-do. These facts strongly suggest that improved hygiene and a rising standard of living may appreciably reduce the incidence of the disease.

As to diagnosis, we face the problem of educating patients to submit to examination, and of training physicians to do proper vaginal examinations. The disease is often missed simply because examination of the cervix is omitted.

In the overwhelming majority of cases its presence is obvious if the cervix is carefully inspected. A biopsy with a simple biting forceps

suffices to prove the diagnosis. Papanicolaou's method of making the diagnosis from smears may eventually come to be valued as a quick method of singling out suspicious cases for more careful study.

Carcinoma of the cervix is, of course, the one disease in which radiation has become the preferred method of treatment. When used expertly about 35 per cent of five year cures can be obtained with it. The reasons for this comparative success of radiation are obvious. The cervix, being a small hollow organ, can be attacked with radiation both from within and from without. The radiation effect which results is intense, and without doubt completely destroys the carcinoma in many cases.

In keeping with the contemporary general trend toward surgery in the treatment of cancer, the radical surgical attack on carcinoma of the cervix has recently been revived by Meigs in Boston. Taylor and Twombley in our own city have also begun to do the Wertheim operation. They perform it on alternate cases and thus can compare its results with radiation. It is significant of the progress of surgical technique that the lowest mortality that Wertheim himself was able to report in 1911, when he had brought his operation to the peak of perfection for his day, was 15 per cent. Meigs and Taylor and Twombley, however, with our modern technical resources have performed the operation in more than a hundred cases without any operative mortality. The great handicap of the Wertheim operation, of course, is that it can be done only in the comparatively early cases, and these constitute only a limited percentage of all those who come for treatment. It is too soon yet to draw any conclusions as to the usefulness of the operation in comparison with radiation.

We can not leave the subject of cancer of the cervix without mentioning the fact that we owe our modern standards for reporting the results of cancer treatment to the European gynecologists. In 1928, under the Cancer Commission of the League of Nations, they drew up a set of rules specifying the data necessary for statistical purposes in reports of cancer treatment. A special point was that no deductions were to be allowed for patients incompletely treated, for those lost track of after treatment, and for those dying of intercurrent disease within the five year period. If this rule were followed by all who report the results of cancer treatment we would today have a great deal more accurate data for comparison of different therapeutic methods.

Cancer of the Skin

Cancer of the skin is today treated in most clinics with radium or x-rays, under the direction of dermatologists or radiologists. Despite the fact that patients with skin cancer usually come for treatment while the disease is limited in extent, and despite its accessibility, a good many recurrences result following radiation as it is generally employed, and we see all too many tragic cases in which very radical and mutilating surgery has finally to be done. Dr. Stout and I, after seeing the comparative results of surgery and radiation, have come to believe that in most instances it is better to attack the disease surgically in the beginning. Our reasons for this can be summed up under three heads.

1. Surgery incapacitates the patient for a shorter time and is therefore more economical. A surgical wound is healed in a week while a radiation reaction persists for a month.

2. Surgery gives a better cosmetic result than radiation. Scars made with modern surgical technique are almost invisible, while the scar resulting from adequate radiation is a depressed white, telangiectatic, easily traumatized area of skin.

3. Surgery is more certain to cure. With the surgical techniques that the plastic surgeons have developed during the last twenty-five years it is possible to excise comparatively large areas of skin and subjacent tissues and to repair the defect by shifting flaps or transplanting skin. This ability to sacrifice tissues generously gives the surgeon an advantage over the radiotherapeutist, who usually limits his field closely around the lesion. The radiotherapeutist, moreover, is at a great disadvantage where the lesion overlies bone or cartilage, for radiotherapy is not successful with epithelioma involving these structures. Finally, when surgical excision is done it is possible for the surgical pathologist to study the depth and extent of the epithelioma in the specimen, and to give the surgeon an accurate estimate of the thoroughness of removal. The radiotherapeutist lacks any such guide, and his treatment is necessarily less exact and more empirical.

An exception to the assignment of skin cancers to the surgeon should be made for skin cancers occurring in the aged and feeble, in whom radiation is preferable.

Cancer of the Stomach

Cancer of the stomach, the fourth most frequent type of cancer,

is a silent enemy that gives no warning of its presence until it is inoperable in the overwhelming majority of patients. Our problem with the disease is a diagnostic one: gastric resection aiming at cure can be done in only about 15 per cent of those who come for treatment. We must find a better method of detecting its presence in an operable stage if we are to make any headway against it.

Gastroscopy is helpful in some cases, but x-ray study is the most reliable method of diagnosis. Its great disadvantage is its expense. In New York today a gastrointestinal series costs from $60 to $75. Oftentimes patients with vague digestive disturbances, over the age of 50, in whom the presence of the disease should be suspected cannot afford such an expensive diagnostic procedure, and it is omitted.

Many patients with cancer of the stomach have no symptoms at all until the disease reaches the inoperable stage. In an effort to pick up these silent lesions, Dr. Paul Swenson, lately of our Clinic, and now at Jefferson Medical School, studied a series of 2413 patients who had no digestive symptoms of appreciable significance. He made a rapid fluoroscopic examination to determine whether the stomach showed any abnormality, and carried out the usual detailed examination only in patients with abnormalities. Two gastric carcinomas and one lymphosarcoma were found in this manner. Both the carcinomas were early and were resected. This abbreviated type of x-ray examination used by Dr. Swenson would seem to offer the only practical means we have at present of diagnosing gastric cancer at a price within the reach of every man. Although radiologists will protest against using any but the most thorough method of examination, I would answer them by saying that it is better to have used an abbreviated inexpensive method of examination than not to have examined the patient at all. A gastric cancer picked up this way means a life saved.

For we must keep in mind that when the patient's lesion is in an operable stage his chance of cure with present day surgical technique is fairly good. The operative mortality for gastric resection has been brought down from 30 per cent to about 5 per cent during the last generation. The patient surviving resection has at least a 25 per cent chance of five year cure. Recently developed surgical techniques are making possible more and more radical gastric resections and we can hope for some further improvement in the cure rate.

Cancer of the Prostate

Carcinoma of the prostate, sixth in order of frequency, is one of the most formidable enemies of old age in men. From the viewpoint of both diagnosis and treatment our methods are very unsatisfactory, and for the moment there seems to be no immediate prospect of improving them. The radical surgical attack is applicable only to a very small group of cases where the disease is confined within the capsule of the prostate gland, and such cases are rarely diagnosed.

All of us were encouraged a few years ago by the results of orchidectomy and of estrogen treatment. We know now, however, that this therapy is only palliative. It prolongs comfort but it apparently does not prolong life.

Summary

As we have traced the general course of our therapeutic attack on cancer during the last fifty years, and illustrated our theme with examples from the most frequent types of cancer, we see that very real progress has been made in the therapeutic attack. But our curative efforts have been greatly limited and restricted by our lack of good methods of early diagnosis, and our inefficiency in using the methods that we have. For the present our best immediate hope of progress in our attack on cancer is better education of physicians in the use of proved diagnostic methods. This means better undergraduate, as well as more and better post-graduate, education. About two-thirds of the physicians practicing in New York City have no connection with any hospital and they lack therefore the normal educational opportunities that hospital practice brings with it. We must help them, and it is with this purpose in mind that we inaugurate the Academy's Graduate Fortnight in Cancer.